UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,049	11/01/2005	Eva Kontselova	SONN:066US	5434

32425 7590 07/20/2009
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/521,049
Filing Date: November 01, 2005
Appellant(s): KONTSEKOVA ET AL.

Travis M. Wohlers
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 13, 2009 and supplemental appeal brief filed on May 04, 2009 appealing from the Office action mailed November 13, 2008 and the Advisory action mailed on January 27, 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is not correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief filed on May 04, 2009 in relation to rejected claims 17-31 has been corrected to rejected claims 17-37 by appellant's supplemental appeal brief filed on May 5, 2009.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Williams et al., *Appl Physiol,* pp. 1119-1126, 2000.
Hammer et al. *J. Anim. Sci,.* pp. 269-278, 1986.
Hammer et al., Cell, pp. 1099-112, 1990 .
Sigmund. *Arterioscler Thromb Vasc Biol*., pp. 1425-9, Review. 2000.
Logan et al., Clinical and Experimental Pharmacology and Physiology, pp.1020-5, Review.1999.
Shuman, Experentia 47, pp. 897-905.1991.
Hrnkova M et al., *Brain Res,.* pp.:206-13. 2007.
Moreadith RW, *J Mol Med*., pp. :208-16. 1997.
Keefer, *Anim Reprod Sci*., pp. 82-83:5-12. Review. 2004.
Kappel, Current Biology, pp. 548-553, 1992
Dudal et al., *Neurobiol Aging*., pp. 861-71. 2004.
Lewis et al. Nature Genetics, pp. 402-405. 2002.
Echeverria et al. *J Alzheimers Dis,.* pp. 209-19. 2004.
Zilka et al., FEBS letters, pp. 3582-3588. 2006.
Huang et al., Brain Research, pp. 213-220. 1997.
Gotz et al., Brain Research, pp. 266-286. Review 2001.
Hartig et al., European Journal of Neuroscience, pp. 69-80. 2007.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic rat whose genome comprises a transgene comprising a DNA construct comprising a cDNA molecule, wherein:

the cDNA molecule is truncated, wherein the truncation starts at least 30 nucleotides downstream of the start codon and wherein the truncation starts at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein,

the cDNA molecule comprising **SEQ ID No. 9**, said cDNA operably linked to a promoter, wherein the promoter is a Thy-1 promoter,

wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology associated with Alzheimer's disease occurs in the rat when compared to normal rats,

does not reasonably provide enablement for any non-human transgenic animal. Additionally, the instant claims do not provide sufficient enablement for any promoter (e.g., constitutive or tissue specific) other than the Thy-1 promoter for the observed phenotype of neurofibrillary pathology in rat brain. The deficiencies were identified by the Office after analysis of the disclosure provided in the instant application.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first

paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The instant claims are broadly drawn to any non-human transgenic animal having germ and/or somatic cells , e.g., hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and others as models to study Alzheimer's disease wherein said transgenic non-human animal comprise a genus of cDNA constructs coding for a N- and C-terminally truncated tau protein molecules including the sequences identified as SEQ ID Nos. 1 to 14 as illustrated in Fig. 1 of the specification as filed, each sequence comprising a minimally truncated tau core identified as SEQ ID No. 9 in Fig. 1, said cDNA constructs able to express a truncated human tau protein producing neurofibrillary (NF) pathology producing activity when expressed in the brain of rats. Additionally, independent claim 17, as written, does no place any limitation on said genus of cDNA molecules comprising SEQ ID No. 9 to be functionally linked to a promoter in order to target expression of the tau gene product to the brain. In contrast, independent claim 37 requires the claimed cDNA molecule to be operably liked to any promoter, however, there is not

limitation requiring a tissue-specific promoter for expression in the brain. Furthermore, independent claim 17 does not specifically convey germline transmission of the transgene and could be broadly interpreted as encompassing merely one somatic cell in any non-human transgene animal that have been transformed with the claimed constructs wherein expression of the tau gene product is sufficient to exhibit a neurofibrillary (NF) pathology producing activity in brain. Moreover, independent 25 is drawn to a screening assay for a cognate drug in the treatment, prevention and diagnosis of a tauopathy comprising validation of the cognate drug in the treatment of hypertension, diabetes, dislipidaemia and/or hypercholesterolemia in combination with the tauopathy. The specification provides insufficient guidance to enable claims directed to the transgenic non-human animals as broadly claimed. Thereby, specific issues related to transgenic non-human animals and corresponding phenotype including unknown predictability of particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) whereby NF pathology producing activity are provided for the claimed transgenic animals having germ and/or somatic cells have to be examined and considered for patentability regarding the broadly claimed products.

At about the effective filing date of the present application (07/09/2003), the transgenic art was and continues to be unpredictable with respect to transgene behavior *in vivo*. Transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, specific promoter/gene combinations, and random transgene insertion. Though transgenic animals have been generated by introducing foreign genes by microinjection into fertilized eggs including mice, sheep and pigs, the same transgene

construct integrated in the chromosome of recipient animals does not necessarily result in the same phenotype. For example, Hammer et al. (*J. Anim. Sci.* 63:269-278, 1986) teaches production of transgenic mice, sheep and pigs, however, only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pp. 276-277, Subsection: Effect of Foreign GH on Growth). Indeed, the author clearly states that even in genetically related species such as rats and mice, the phenotypes resulting from integration of the same genetic construct is unpredictable (Cell, 1990, 63: 1099-112; p. 1099, column 2, lines 20-28). Furthermore, even strain differences among mice carrying the same construct can profoundly influence the phenotype (Sigmund et a., *Arterioscler Thromb Vasc Biol*, 2000, p. 1425, col. 1, paragraph 2). Sigmund states,

> "For example, whereas deletion of p53 tumor suppressor gene causes a dramatic increase in the frequency of tumor formation in those mice compared to the wild type, the type of tumors formed, their number per animal, and age of tumor onset vary in different genetic backgrounds."

Likewise, the expression of the same Amyloid Precursor Protein (APP) transgene in closely related rodents such rats and mice produces distinct phenotypes. For example, expression of an Amyloid Precursor Protein (APP) transgene at sufficient level to serve as a model for neurofibrillary tangles, neural lesions and Alzheimer's disease (AD) in rats produces what is referred to as "preplaques" (Echeverria, page 217, and col. 2, lines 4-9). This is in stark contrast to transgenic mice expressing APP SWE/Indiana transgenes. These mice exhibit ThioS positive fibrillar and non-fibrillar plaques, but at a much earlier age than other mice (Dudal, page 868, col. 1, parag. 1, lines 17-19 and parag. 3, lines 1-3). Conversely, presence of neurofibrillary tangles (NF) tangles is not merely associated with just Alzheimer's disease but with widely divergent neurodegenerative diseases in addition to Alzheimer's disease. For example, Lewis et

al., (2000) teaches the pleitropic role of neurofibrillary tangles prominent not only in Alzheimer's disease but in Pick disease, progressive supranuclear palsy parkinsonism and corticobasal degeneration (Abstract). Thus expression of the tau gene product in a subject is associated with other unrelated diseases. This would show that simply finding a difference in expression of the tau gene product is not indicative of diagnosis of Alzheimer's disease in particular

Post filing art by Keefer et al., (2004, Animal Reproduction Science, pp. 5-12) brings similar insight into the lack of predictability of generating any transgenic animal as the author recognizes the inefficiency of pronuclear microinjection in transgenic techniques resulting in mosaic animals with some cells containing the transgene and others not, and the unpredictability of transgene expression when applied to generating cows, goats and sheep (p.6, last paragraph bridging to p. 7, paragraph 1). The unpredictability associated with the generation of non human transgenic animals incorporating the same gene construct but expressing a different phenotype can be explained by a plethora of intrinsic differences across the species, such as promoter/enhancer elements, co-regulatory factors that may be present in one species and not another, or the existence of redundant pathways in one species versus another that can lead to differences in phenotype (Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p. 1124, col. 2, paragraph 2). Moreover, specific genetic modification is strongly influenced by genes unlinked to the targeted locus (Sigmund et al., Arterioscler Thromb Vasc Biol, 2000, pp. 1425- 1429). Because of the random integration of the foreign DNA without preference for a particular chromosomal location, Logan et al., (1999, Clinical and Experimental Pharmacology and Physiology, p. 1021, col. 2, paragraph 2) anticipates that the challenge in the development of

transgenic animals in not in the process, but the design of the construct that will allow for the expression of the gene of interest in the desired cell type at an appropriate level (e.g., control under a tissue-specific promoter). Furthermore, the claims broadly embrace any non human transgenic including transgenic birds, as such, Shuman (Experientia 47, pp. 897-905, 1991) teaches that the avian technology for gene transfer for production of transgenic birds has not progressed as much as mammalian gene transfer, in part, by the avian reproductive and embryonic developmental system requiring considerable testing and evaluation (p. 897, col. 1, paragraph 1). Likewise, in relation to the generation of transgenic animals by using stem cells (ES) to carry the foreign gene rather producing transgenic mice by microinjection into fertilized eggs, the art is highly unpredictable. For example, Moreadith et al., (1997, J Mol Med pp. 208-216) teaches that several putative ES cells lines have been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but the technology was limited to mice (page 214, col. 1, paragraph 3, lines 5-12). Hence the art is unambiguously unpredictable in relation to the generation transgenic birds, hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and others by integration into their chromosome of a gene of interest either by microinjection or using ES cells evidencing that the phenotype in one species cannot obviate an identical or even similar phenotype in the compared species, even within the same species.

Insofar as the expression of a transgene, it was also well known in the art at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter that controls gene expression (Kappel, Current Biology, 1992, entire document, specifically, p. 349, col. 2 paragraph 1). Additionally, it was well known in the art that no all promoters result in efficient expression or expression at levels in the appropriate

tissues to result in a phenotype that is useful (Williams et al., (*J. Appl. Physiol.,* 2000, p. 1124, col.2, lines 15-19). In other words, a transgene which expression is tissue specific, e.g., brain, may be present in other tissues in a transgenic mice but said gene may not be regulated, in part, because regulatory factors that may be present in the brain and not another tissues. Conversely, use of a constitutive CMV promoter in mice which is active in a wide range of tissues and drives high-level constitutive expression will generate a transgenic non-human animal exhibiting global expression of the truncated tau gene that will necessarily result in a different transgene phenotype from a expression of the same gene under the control of a tissue-specific promoter, e.g., Thy-1. Therefore, it is clearly set forth in the art the required linkage of a gene to a promoter and selection of tissue specific promoters for effective expression of a gene of interest in tissue specific manner. Hence, it would require undue experimentation for the skilled artisan to express the gene product of the claimed DNA construct under the control of any promoter other than the Thy-1 promoter to result in the claimed NF pathology producing activity when the cDNA construct is expressed brain cells. Furthermore, in relation to the breadth of the claims to any transgenic, the claims may be interpreted to read on somatic cell gene transfer. It would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype in the brain cells of the transgenic non-human animal. Applicants have not provided any evidence of transgenic non-human animals having solely germ cells or somatic cells exhibiting the claimed phenotype. In other words, Applicant have disclosed a single founder mouse forming line #318 wherein every member of the cell line has the same truncated tau gene at the identical position.

Indeed, generation of the transgenic founder line #318 is disclosed in the specification at pages 21-22 (Fig. 1) with the initial creation of a transgene construct that was prepared by ligation of a cDNA coding for the human tau protein truncated at amino acid positions 277–991 (i.e., SEQ ID NO: 3) downstream the mouse Thy-1 gene, e.g., the brain promoter/enhancer sequence. Rats stably expressing human truncated tau were createdby pronuclear injection of one-day old rat embryos which generated transgenic founder line #318. Moreover, the specification teaches expression of Alzheimer's tau proteins in the brain of transgenic rats by Western analysis and localizes by immunohistochemistry said proteins in brain tissue sections (pp. 24 and 25). Furthermore, the specification contemplates the use of the transgenic animals for *in vitro* and *in vivo* systems for the study of drug candidates on cell architecture, cell division and apoptosis as well as morphology of primary cultured neurons, and of organelle movement (p. 25, paragraph 1, and FIG. 9). Additionally, the 2nd Filipcik Declaration evidences creation of transgenic rat # 24 which contains the construct comprising nucleotides 277-906 of tau of SEQ ID No. 12 (2nd Filipcik Declaration, page 2, paragraph 4) and the third Filipcik Declaration evidences generation of the transgenic rat line #72 coding for 4-repeat and 3-repeat tau protein comprising nucleotides 277-999 of tau of SEQ ID No. 3, which is the same construct used in the generation of transgenic rat # 318 (3rd Filipcik Declaration, page 2, paragraph 5). While the instant specification teaches that transgene expression was detected for expression Alzheimer's tau proteins in the brain of transgenic rats by Western analysis and corresponding proteins were localized by immunohistochemistry in tissue sections, the specification fails to provide any correlation between expressions of any Alzheimer's tau proteins in rat with any useful phenotype including hypertension, diabetes, hypercholesterolemia as broadly claimed. There is not evidence

that hypertension, diabetes, hypercholesterolemia is uniquely associated with expression of a truncated tau protein. As hypertension, diabetes, hypercholesterolemia may be associated with diseases other than Alzheimer, the simply expression of a truncated human tau protein producing neurofibrillary (NF) pathology producing activity and detection of changes of neurofibrilllar pathology in brain cells of a transgenic animal along with diagnosis of hypertension, diabetes, hypercholesterolemia is not indicative of a tauopathy in particular. In fact, post filing art by the inventors states, "in human sporadic Alzheimer's pathology, mature neurofibrillary degeneration is characterized by extensive formation of sarcosyl insoluble tau protein complexes" (Zilka et al., FEBS letters, 2006, p. 3587, col. 1, last paragraph) and "The present study provides the experimental data introducing truncated tau protein as an important upstream factor in the pathogenesis of neurofibrillary degeneration of AD type" (p. 3587, col. 2, last paragraph), clearly indicating that the observed pathological changes are just one of the multiple factors leading to Alzheimer's disease.

As enablement requires the specification to teach how to make and use the claimed invention, based on the instant disclosure a skilled artisan, particularly in light of the state of the transgenic art which was and continues to be highly unpredictable with respect to incorporation and expression of a transgene and the resulting corresponding phenotype in any species of animal, as discussed above, one skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species of non-human transgenic animals, with the claimed phenotype to describe the genus.

Claim Objection

Claims 17-37 remain objected to because of the following informalities. Claim 17 and 37 recite, "the molecules have truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence". It is unclear whether the first 30 nucleotides of the full length tau cDNA sequence downstream the start site are truncated or the truncation begins at the 30 nucleotide position downstream of the start codon. Similarly, it is unclear whether the truncation 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence includes the 30 nucleotides upstream of the stop codon or the truncation begins at the 30 nucleotide position upstream of the stop codon. Appropriate correction is required.

(10) Response to Argument

Appellant's arguments have been addressed in the order in which they have been presented in the appellant's appeal brief.

A. Claims are enabling.

At page 3 of the Appeal Brief, Appellant essentially argue that the Examiner's concern about variability of transgene expression in different animals or under the control of different promoters are misplaced with respect to independent claims 17 and 37 because these claims do not require any amount of truncated tau protein to be expressed in the brain of animals. Appellant's arguments have been fully considered, but are not found persuasive.

The instant claims have been examined in accordance with the *Wands* factors and the teachings of the specification **as a whole.** Though independent claims 17 and 37 only require the production neurofibrillary (NF) pathology producing activity when the truncated human tau product is expressed in the brain, the specification as filed does not provide an enabling

disclosure for other pathologies associated with expression of a truncated human tau in germ and /or somatic cells, other than detection of intracellular inclusions and neurofibrillary filaments (e.g. neurofibrillary tangles) in brain sections from transgenic animals as compared with non-transgenic animals, clearly resulting from expression of the truncated human tau protein in brain (Examples 4 and 5). Note that neurofibrillary tangles are one of the major hallmarks of Alzheimer's disease. Hence, the present issue of enablement is whether the scope of the patent protection sought by the Applicant as defined by the claims correlates with the scope of enabling disclosure set forth in the specification. In other words, is there sufficient guidance to make and use any transgenic non-human transgenic animal having germ and/or somatic cells comprising a cDNA encoding a truncated tau protein exhibiting a NF pathology producing activity when the truncated tau protein is expressed in brain cells?

1. The transgenic non-human animal

a) The specification provides an enabling disclosure for how to make and use a transgenic non-human animal, **b)** Transgenic Rat Lines #24, #72, and SHR24/72, **c)** Many animals exhibit the neurofibrillary pathology associated with Alzheimer's disease.

. At pages 4-9 of the Appeal Brief, Appellant essentially argues that: **a)** in addition to the generation of the transgenic rat line #318 which expresses the human truncated tau protein encoded by the tau cDNA sequence compromising SEQ ID NO. 9, said rat line #318 exhibiting tau-related neurofibrillary pathology in the brain, the declaration of by Dr. Peter Filipcik executed on August 1, 2007 (1st Filipcik Declaration, paragraph 11) evidences that expression of truncated tau in transgenic rat line #318 also exhibits other pathological features associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes,

b) in addition to transgenic rat line #318, other transgenic rats have been generated including transgenic rat **# 24** containing the construct comprising nucleotides 277-906 of tau of **SEQ ID No. 12** (2nd Filipcik Declaration, page 2, paragraph 4) and transgenic rat line **#72** comprising a cDNA sequence coding for 4-repeat and 3-repeat tau protein comprising nucleotides 277-999 of tau of **SEQ ID No. 3,** which is the same construct of transgenic rat # 318 (3rd Filipcik Declaration, page 2, paragraph 5). The phenotype of the three transgenic rat lines **#318, #72 and #24** is almost identical. The only observed difference among the three transgenic rat lines **#318, #72 and #24** has been that the life span of those animals containing 4 repeat tau (e.g. Tg line #72) is much shorter when compared to those animals containing 3 repeat tau region (e.g. Tg line #24) of human tau protein (Third Filipcik Declaration, para. 6). Moreover, Appellant alleges that the phenotype produced by transgenic truncated tau expression was not dependent on genetic background as the transgenic rats belong to different genetic backgrounds, e.g. hypertensive SHR strain (#72) and normotensive Wistar strain (WKY). Thus, Appellant argues that there is sufficient evidence for a transgenic non-human animal having germ and/or somatic cells with a reproducible phenotype that can be achieved from different insertional events and different animal strains, **c)** other animals in addition to rats are suitable models for Alzheimer's disease including transgenic mice (Lewis et al., Nat Genet, 2000), which express the P301L mutant tau, hamsters and ground squirrels (Hartig et al., Abstract), rabbits (Huang et al., Brain Research, 1997), several transgenic animals models including mice and lamprey (Gotz et al., Brain Research Review 2001). Appellant's arguments have been fully considered, but are not found persuasive.

Regarding a), the fact that transgenic rat line #318 exhibits other pathological features that may be associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes is not disputed. However, Appellant fails to provide any useful correlation of the claimed phenotypes associated with Alzheimer's disease e.g., hypertension, diabetes, hypercholesterolemia such that one of skilled in the art could make and use a transgenic non-human animals in any of the contemplated treatment, prevention and/or diagnosis of a tauopathy in a useful way. In other words, are gene mutations leading to progressive neurobehavioral impairment in Alzheimer's disease in humans the same as in the claimed transgenic non-human animals encoding a truncated tau protein and exhibiting the claimed phenotypes? How is the observed phenotype of hypertension, diabetes, hypercholesterolemia correlated in any useful way with prevention and/or diagnosis of Alzheimer's disease? As hypertension, diabetes and hypercholesterolemia are associated with diseases other than a tauopathy such as Alzheimer's, the simply expression of a truncated human tau protein producing neurofibrillary (NF) pathology producing activity and diagnosis of hypertension, diabetes, hypercholesterolemia may not be indicative of a tauopathy in particular. Conversely, presence of NF tangles in brain cells is not merely associated with Alzheimer's disease but with widely divergent neurodegenerative diseases including Pick disease, progressive supranuclear palsy, Parkinsonism and corticobasal degeneration. Thus detecting changes in NF tangles along with neurobehavioral changes in a transgenic animal may be indicative of other neurodegenerative diseases in addition to Alzheimer's disease. Hence there is not a reasonable correlation between scope of patent protection sought by the Applicant as defined by the claims

and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel*.). How can such a broadly claimed transgenic non-human animal be made and used without undue experimentation when there is no supporting evidence to substantiate a reasonable correlation between any transgenic non-human animal having germ and/of somatic cells which comprise a truncated cDNA encoding a truncated tau protein and any treatment, prevention and/or diagnosis of any tauopathy including Alzheimer's disease in any useful way?

Regarding b) the generation of three transgenic founder rat lines **#318, #72 and #24** comprising a DNA construct comprising a cDNA molecule, wherein: the cDNA molecule is truncated, wherein the truncation starts at least 30 nucleotides downstream of the start codon and wherein the truncation starts at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein, the cDNA molecule comprising **SEQ ID No. 9**, said cDNA operably linked to a promoter, wherein the promoter is a Thy-1 promoter, is not disputed. However, there is not sufficient evidence for any transgenic non-human animal having germ and/or somatic cells with a reproducible phenotype that can be achieved from different insertional events. The specification, the three declarations signed by Dr. Filipcik and post filing art by Applicants indisputably disclose the creation of three independent transgenic founder lines e.g., **#318, #72 and #24** that stably expressed human truncated tau displaying similar phenotype. A single founder mouse which forms a line of mice requires every member of a line to have the same transgene at the identical positioning its genome. Additionally, a transgenic founder line requires the stably integration of the cDNA molecule comprising SEQ ID No. 9 in both the somatic and germ cells. Applicants have not provided any evidence of transgenic non-human animals having solely germ cells or somatic cells exhibiting

the claimed phenotype. Fore example, the claims may be interpreted to read on somatic cell gene transfer. It would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype when the cDNA gene product encoding a truncated tau is expressed in brain cells of the transgenic non-human animal. At the most, applicants have sufficient disclosure for a transgenic rat whose genome comprises a transgene comprising a DNA construct comprising a cDNA molecule encoding for the truncated tau wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology associated with Alzheimer's disease occurs in the rat when compared to normal rats.

Regarding c), Lewis et al., (2000) clearly teaches the pleitropic role of neurofibrillary tangles in mice expressing the human tau containing the most common FTDP-17 mutation (P301L) , resulting not only in Alzheimer's disease but in Pick disease, progressive supranuclear palsy, and corticobasal degeneration (Abstract). Clearly, NF tangles are associated with widely divergent neurodegenerative diseases in terms of their pathologic mechanisms in addition to Alzheimer's disease. There is not evidence that the phenotype of transgenic mice expressing the P301L mutant tau correlates with the NF pathology producing activity including hypertension, diabetes, and hypercholesterolemia of the transgenic founder lines e.g., **#318, #72 and #24** that stably expressed human truncated tau as broadly claimed in the instant invention. In relation to the Hartig et al., (2007) disclosure, the examiner notes that the effective filing date of the present application is July 12, 2002. As stated in the previous office action filed on 11-13-2008 at pages 7-8, post-filing art of Hartig et al. (2007), cannot be used to show what was known at the time of filing. The Huang et al., (1997) reference is not related to a non-transgenic animal as the

disclosure describes induction of neurofibrillary tangles of Alzheimers' disease by administration of an agent effective in inducing neurofibrillary degeneration in rabbit. Thus the Huang et al., reference is not relevant to the raised enabling issues related to the generation of transgenic non-human animals. While the disclosure of Gotz et al., (2001), teaches murine models including transgenic mice for the study of Aβ peptide containing plaques and neurofibrillary aggregates of isoforms of tau protein, the author also teaches that two mechanisms that appear to be responsible for neurodegeneration and dementia, namely mutations in the amyloid precursors protein APP, from which the Aβ peptide is derived and Tau filament formation. Indeed, Tau in the absence of Aβ peptide production exhibit other neurodegenerative disorders including supranuclear palsy, parkinsonism linked to chromosome 17, corticobasal degeneration, and others (Abstract). Additionally, Gotz discloses that sea lamprey, a parasitic fish, has been used as a model for neurofibrillary degeneration which also is present in Alzheimers' disease, however, significant differences are present between tau deposit in humans and sea lamprey (p. 272, col. 1, last paragraph). Therefore, there is not evidence in the disclosure of Hartig et al. Huang et al., Gotz, and Lewis, for enablement of non-human transgenic animals having germ and/or somatic cells such animals exhibiting characteristics that make them suitable models for Alzheimer's disease, let alone any tauopathy.

d) The references cited in the action.

At pages 9-13 of the Appeal Brief, Appellant essentially argues that: **a)** Williams (2000; Exhibit 1) teaches that limitations related to transgene expression in different species of transgenic non-human animals and variability in phenotypes among strains were conventional practice in the art and enablement is not precluded by the necessity for some experimentation

such a routine screening, 2) Moreadith (1997; Exhibit 2) primarily discusses the generation of transgenic animals from embryonic stem cells (ES cells), however, the instant invention is not limited to transgenic generated by ES cell techniques but also by introducing foreign genes by microinjection into fertilized eggs. Moreover, applicants only need to provide an enabling disclosure of the claimed invention, 3) Keefer (2004; Exhibit 3), teaches the inefficiency of pronuclear microinjection in generating transgenic animals, however, the inefficiency can not be equated with unpredictability. Moreover, the Keefer's reference is unrelated to the instant invention because Keefer concern is related to whether the transgenic animal will express the desired protein in large amount for byproducts in livestock and not on creating an animal model for a disease, 4) Sigmund (2000; Exhibit 4) teaches that specific phenotypes are affected by genetic modification of genes unlinked to the target locus, however, as already discussed for Williams, the unpredictability associated with potential variability in transgenic animals in the Sigmund's publication is considered routine in the art. Appellant's arguments have been fully considered, but are not found persuasive.

Regarding 1) and 4), the mere recitation that it is "conventional practice" for the skilled artisan to deal with the variability of a method to generate transgenic animals does not render the instant invention enabled, as the skilled artisan will have to engage in undue experimentation to determine unknown predictability of particular host species, specific promoter/gene combinations, random transgene insertion and genetic imprinting (e.g., transcriptional silencing of a gene based on transmission from parent to offspring of repressive nucleosomal structures) whereby NF pathology producing activity are provided for the claimed transgenic having germ and/or somatic cells (Williams et al., J. Appl. Physiol. 2000, p. 1125, col. 1, paragraph 3 and p.

1124, col. 2, paragraph 2) . Thus, given the paucity in the art regarding the claimed transgenic-human animal comprising a construct expressing a truncated tau protein one skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Regarding 2), the fact the applicant needs to provide only one enabling disclosure for the invention is not disputed. However, the Moreadith reference not only refers to the unpredictability of generating transgenic hamster, pig, sheep, cattle, rabbit, rat, mink, and monkey by using ES cells but also to the unpredictability of transgenics generated by introducing foreign genes by microinjection into fertilized eggs. Indeed, in relation to the later technique, Moreadith states, "traditional gain-of function" mutation, typically created by microinjection in relation to the specific target of the gene of interest into the one celled zygote, as an art more unpredictable than the transgenic technology, wherein the gene is targeted via homologous recombination in stem cells (Abstract). Applicants have not provided any evidence or expectation that the claimed transgenic non-human animals generated by any transgenic technology having germ and/or somatic cells and exhibiting NF pathology producing activity is any more or less than the expectation from the teachings of Moreadith and the other prior art documents.

Regarding 3), post filing art by Keefer et al., brings similar insight into the lack of predictability of generating any transgenic animal as the author recognizes the inefficiency of pronuclear microinjection in transgenic techniques resulting in mosaic animals with some cells containing the transgene and others not, and the unpredictability of transgene expression when applied to generating cows, goats and sheep (p.6, last paragraph bridging to p. 7, paragraph 1).

The instant issue of enablement is whether any transgenic non-human animal comprising a genus of cDNA constructs coding for any N- and C-terminally truncated tau protein molecules including sequences of SEQ ID No. 1-14 as illustrated in Fig. 1, exhibiting NF pathology can be generated without undue experimentation, as such post filing art by Keefer et al., clearly discloses lack of predictability on generating any transgenic animal including cows, goats and sheep by microinjection resulting in mosaic animals. Furthermore, the breadth of the claims read on somatic cell gene transfer leading to mosaic animals, it would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype in the brain cells of the transgenic non-human animal. Applicants have not provided any evidence of transgenic non-human animals having solely germ cells or somatic cells exhibiting the claimed phenotype. Appellant's arguments related to whether the transgenic animal will express the desired protein in large amount for byproducts in livestock are not on point.

2. Promoters

At pages 13-16 of the Appeal Brief, Appellant essentially argues that: **1)** at the time the invention was made, functional linkage of a gene of interest to a promoter for expression in a target tissue was well known in the art and it would be undue experimentation for a person of ordinary skill in the art to make and use the claimed invention as embraced in claims 17 and 25, 2) in view of the disclosure in the specification, a person of ordinary skill in the art would know that a "DNA construct" as recited in claim 17 contains a promoter operably linked to the cDNA molecule coding for N- and C-terminally truncated tau molecules, 3) a person of ordinary skill in the art would know that the promoter in the DNA construct in suitable for expression in

mammalian cells as the specification teaches methods for preparation and evaluation of DNA constructs inducing promoters for brain expression and ubiquitous expression (Specification, p. 12, lines 12-38; page 21, lines 8-36), 4) promoters to drive expression of transgenic tau in mice where known in the art as evidence in the disclosure of Lewis et al., (2000), Gotz (2001) Fitzsimons et al (2002) requiring only cloning procedures disclosed in the specification which is routine in the art and does not constitute undue experimentation. Appellant's arguments have been fully considered, but are not found persuasive.

Regarding 1) and 4), the fact that a gene requires functionally linkage to a promoter e.g., constitutive or tissue specific, to be targeted to a tissue and expressed is not disputed. Moreover, it was known in the art that no all promoters result in efficient expression or expression at levels in the appropriate tissues to result in a phenotype that is useful. The instant claims are broadly drawn to any non-human transgenic comprising a cDNA molecule coding for N- and C-terminally truncated tau molecules said transgenic able to exhibit a NF pathology producing activity when express in the brain cells of the animal. As expression of the DNA construct in brain requires a brain-specific promoter to be regulated by factors that are not present in other tissues to exhibit the claimed phenotype, there is not sufficient disclosure for the skilled artisan to make and use a transgenic rat using any promoter, let alone any non-human transgenic animal. For example, use of a constitutive CMV promoter in mice which is active in a wide range of tissues and drives high-level constitutive expression will generate a transgenic non-human animal exhibiting global expression of the truncated tau gene that will necessarily result in a different transgene phenotype from a expression of the same gene under the control of a tissue-specific promoter, e.g., Thy-1.

Regarding 2) and 3) , the manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology (Specification, p. 12, lines 12-38; page 21, lines 8-36). However, the ability to determine *a priori* whether a promoter will target expression of a functional protein to a tissue is not. The breadth of the claims encompass any non-human transgenic animal including birds, reptiles and others in addition to mammalian. Due to the lack of the direction for sequences responsible for brain-specific regulation of a truncated tau gene resulting in the claimed transgenic phenotype, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve the specific claimed phenotype for any non-human transgenic animal as models to study Alzheimer's disease.

3. Claims 19 and 37 are separately patentable

At pages 16-17 of the Appeal Brief, Appellant essentially argues that claims 19 and 37 do not contain a limitation on the amount of transgene expression. Moreover, Appellant alleges that the only basis for rejection of claims 19 and 37 is lack of enablement of promoters that could drive the expression of the cDNA molecule, and because claims 19 and 37 do not contain a limitation on the amount of transgene expression the claims are enable. Appellant's arguments have been fully considered, but are not found persuasive.

The instant claims have been examined in accordance with the *Wands* factors and the teachings of the specification **as a whole.** Though independent claims 17 and 37 only require the production neurofibrillary (NF) pathology producing activity when the truncated human tau product is expressed in the brain cells of rats, the specification as filed does not provide an enabling disclosure for other pathologies associated with expression of a truncated human tau in

germ and /or somatic cells other than detection of intracellular inclusions and neurofibrillary filaments (e.g. neurofibrillary tangles) in brain sections from transgenic rats as compared with non transgenic animals, clearly resulting from expression of the truncated human tau protein in brain. Furthermore, independent claim 17 does not specifically convey germline transmission of the transgene and could be broadly interpreted as encompassing merely one somatic cell in any non-human transgene animal that have been transformed with the claimed constructs wherein expression of the tau gene product is sufficient exhibit neurofibrillary (NF) pathology producing activity in brain. Though claim 37 requires the claimed cDNA molecule to be operably liked to a promoter, there is not limitation requiring a tissue-specific regulation in the brain.

4. Claim 34 is separately patentable

At page 17 of the Appeal Brief, Appellant essentially argues that claim 34 depending from claim 17 requires that the non-human transgenic is a mouse. Because the specification successfully teaches the generation of transgenic rodents and transgenic mice expressing the P301L mutant tau, which phenotype mimics features of human tauopathies, it would require undue experimentation for one of ordinary skill in the art to make and use the transgenic non-human mouse. Appellant's arguments have been fully considered, but are not found persuasive.

At the outset the examiner notes that claim 34 depending on claim 17 is drawn to transgenic non-human mouse having germ and/or somatic cells. As set forth in the paragraph above, claim 17 does not specifically convey germline transmission of the transgene and could be broadly interpreted as encompassing merely one somatic cell. It would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype when the cDNA

gene product encoding a truncated tau is expressed in the brain cells of the transgenic non-human animal. Additionally, the expression of the same Amyloid Precursor Protein (APP) transgene in closely related rodents such rats and mice produces distinct phenotypes. For example, expression of an Amyloid Precursor Protein (APP) transgene at sufficient level to serve as a model for neurofibrillary tangles, neural lesions and Alzheimer's disease (AD) in rats produces what are referred to as "preplaques" (Echeverria, page 217, and col. 2, lines 4-9). This is in stark contrast to transgenic mice expressing APP SWE/Indiana transgenes. These mice exhibit ThioS positive fibrillar and non-fibrillar plaques, but at a much earlier age than other mice (Dudal, page 868, col. 1, parag. 1, lines 17-19 and parag. 3, lines 1-3). At the most, applicants have sufficient disclosure for a transgenic rat whose genome comprises a transgene comprising a cDNA constructs coding for a N- and C-terminally truncated tau protein molecules including the sequences identified as SEQ ID Nos. 1 to 14 as illustrated in Fig. 1 of the specification as filed, each sequence comprising a minimally truncated tau core identified as SEQ ID No. 9 in Fig. 1, said cDNA constructs wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology associated with Alzheimer's disease occurs in the rat when compared to normal rats.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Maria G. Leavitt
/Maria G Leavitt/
Examiner, Art Unit 1633

Conferees:

/Joseph Woitach/
Supervisory Patent Examiner 1633

/Peter Paras/
Supervisory Patent Examiner 1632